Allelic Exclusion and Peripheral Reconstitution by TCR Transgenic T Cells Arising From Transduced Human Hematopoietic Stem/Progenitor Cells.

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Authors: Francesca Giannoni, Cinnamon L Hardee, Jennifer Wherley, Eric Gschweng, Shantha Senadheera, Michael L Kaufman, Rebecca Chan, Ingrid Bahner, Vivian Gersuk, Xiaoyan Wang, David Gjertson, David Baltimore, Owen N Witte, James S Economou, Antoni Ribas, Donald B Kohn

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Public Summary:
This study provides evidence that inserting T cell receptors (TCR) into human blood stem cells allows to reconstitute a cancer-fighting immune system in a mouse. The inserted TCRs have the additional benefit of inhibiting the recombination of endogenous TCRs in T cells of the immune system, which provides for higher expression and no mispairing of TCR chains in immune cells.

Scientific Abstract:
Transduction and transplantation of human hematopoietic stem/progenitor cells (HSPC) with the genes for a T-cell receptor (TCR) that recognizes a tumor-associated antigen may lead to sustained long-term production of T cells expressing the TCR and confer specific antitumor activity. We evaluated this using a lentiviral vector (CCLc-MND-F5) carrying cDNA for a human TCR specific for an HLA-A*0201-restricted peptide of Melanoma Antigen Recognized by T cells (MART-1). CD34(+) HSPC were transduced with the F5 TCR lentiviral vector or mock transduced and transplanted into neonatal NSG mice or NSG mice transgenic for human HLA-A*0201 (NSG-A2). Human CD8(+) and CD4(+) T cells expressing the human F5 TCR were present in the thymus, spleen, and peripheral blood after 4-5 months. Expression of human HLA-A*0201 in NSG-A2 recipient mice led to significantly increased numbers of human CD8(+) and CD4(+) T cells expressing the F5 TCR, compared with control NSG recipients. Transduction of the human CD34(+) HSPC by the F5 TCR transgene caused a high degree of allelic exclusion, potently suppressing rearrangement of endogenous human TCR-beta genes during thymopoiesis. In summary, we demonstrated the feasibility of engineering human HSPC to express a tumor-specific TCR to serve as a long-term source of tumor-targeted mature T cells for immunotherapy of melanoma.Molecular Therapy (2013); doi:10.1038/mt.2013.8.